Please add the following new claim.

5. *(New)* A method for reducing side effects of a CpG-containing phosphorothioate oligonucleotide administered to a mammal, comprising:

(a) providing a CpG-containing phosphorothioate oligonucleotide having a CpG modification selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG; and

(b) administering the modified CpG-containing phosphorothioate oligonucleotide to the mammal, wherein administration of the modified CpG-containing phosphorothioate oligonucleotide results in fewer side effects than the administration of an unmodified CpG-containing phosphorothioate oligonucleotide.

Remarks

Claims 1-4 are pending in the application. The Advisory Action mailed on September 10, 2002 indicates that Applicant's amendment filed on June 11, 2002 has not been entered and the exhibits submitted therewith have not been considered. Applicant submits herewith a Request for Continued Examination in order to gain entry of the foregoing amendment and consideration of the exhibits submitted herewith.

Claims 1, 3, and 4 have been amended. Claim 2 has been canceled, the subject matter of claim 2 having been incorporated into independent claim 1. New claim 5 has been added. No new matter has been added by way of these amendments. Support for the amendment of claims 1, 3, and 4 can be found, for example, on page 10, line 18, to page 13, line 20, and Example 2. Support for new claim 5 can be found throughout the application as filed. More particularly, support for new claim 5 is found in Example 2, 3, and 4, which demonstrate that the administration of modified phosphorothioate antisense oligonucleotides results in fewer side affects than therapies utilizing phosphorothioate oligos that have not been modified. Upon entry of the foregoing amendment, claims 1, 3, 4, and 5 will be pending in the application.

1. *Rejection Under Doctrine of Obviousness-Type Double Patenting*

On page 2 of the Final Office Action, claims 1-3 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 of U.S. Patent No. 5,856,462.

Upon a finding by the Examiner that the pending claims are otherwise patentable, a Terminal Disclaimer will be filed disclaiming the portion of the term of the patent beyond the expiration of U.S. Patent No. 5,856,462.

2. *Amended Claims 1, 3 and 4 Are Not Indefinite Under 35 U.S.C. § 112, Second Paragraph.*

Claims 1-4 stand rejected under 35 U.S.C. § 112 as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. At page 2, the Final Office Action indicates that the claim language "compositions of matter" seems redundant and amendment to refer to "compositions" would be remedial.

Applicant thanks the Examiner for making this observation. Applicant has amended the claims to remove the redundant language, the amended claims referring now to "compositions." Applicant respectfully requests withdrawal of the outstanding rejection in view of this amendment.

3. *Amended Claim 1 Is Enabled Under 35 U.S.C. § 112, First Paragraph.*

Claim 1 stands rejected under 35 U.S.C. § 112, first paragraph, on the grounds that the specification is not enabling for CpG oligos having reduced side effects for oligos simply having phosphorothioate linkages. At page 2, the Final Office Action states that the specification is enabling for reduced side effects with CpG oligos having the modifications of claim 1 and/or those shown in Example 2.

In response, Applicant has amended the claim to recite CpG modifications disclosed in the specification, *i.e.* alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG.

In view of the amendment, Applicant respectfully requests reconsideration and withdrawal of the rejection of claim 1 under 35 U.S.C. § 112, first paragraph.

4. ***Amended Claims 3 and 4 Are Enabled Under 35 U.S.C. § 112, First Paragraph.***

Claims 3 and 4 stand rejected under 35 U.S.C. § 112, first paragraph. The Office Action states at page 3 that the specification is not enabling for (1) methods in whole organisms and for (2) oligos simply having phosphorothioate linkages as in claim 1. The Office Action further states that the specification is enabling for methods in cells in culture and for reduced side effects for oligos having the modifications listed in claim 2 and/or those shown in Example 2.

With regards to the basis of the rejection regarding oligos simply having phosphorothioate linkages, Applicant has amended claim 1, upon which claims 3 and 4 depend, to recite modifications disclosed in the application, *e.g.*, Example 2, for oligos with reduced side effects. This issue is addressed *supra* in response to the rejection of claim 1 under 35 U.S.C. § 112, first paragraph.

Accordingly, Applicant respectfully requests that the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

Applicant traverses the rejection of claims 3 and 4 under 35 U.S.C. § 112, first paragraph, on the basis that the specification is not enabling for methods in whole organisms. The instant Office Action further states that the rejection is made for the same reasons as set forth in the Office Action mailed September 9, 1999, which states, *inter alia*, on page 4 that "The ability to determine regions of accessibility and delivery regimes *in vivo* for antisense oligos such that any desired target gene can be successfully inhibited and/or treatment effects be provided remains highly unpredictable in the art."

Applicant respectfully disagrees. M.P.E.P § 2164.01 states that 35 U.S.C. § 112, first paragraph, "has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation." The same section further states that "[t]he fact that experimentation

may be complex does not necessarily make it undue, if the art typically engages in such experimentation." M.P.E.P § 2164.02 states that "[a]n *in vitro* or *in vivo* animal model example in the specification, in effect, constitutes a 'working example' if that example 'correlates' with a disclosed or claimed method invention. . . . In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate." This section further states that a "rigorous or an invariable exact correlation is not required." M.P.E.P § 2164.03 relates to the relationship of predictability of the art and the enablement requirement; this section states that "what is known in the art provides evidence as to the question of predictability."

Applicant submits that one of ordinary skill in the art would know how to determine effective antisense oligonucleotides without undue experimentation. For example, Milner *et al.* (*Nature Biotechnology* (1997) **15**:537-541; attached hereto as Appendix A), demonstrates "a combinatorial technique that allows simultaneous assessment of all possible [oligonucleotides ("ONs")] within a given region identifying sequences open to duplex formation. An oligonucleotide 'scanning' array reduces the number of synthesis steps while providing a parallel and exhaustive analysis of all ONs in the region to be targeted." (page 537) This article further states that "those ONs which give high duplex yield on the array proved to be effective antisense agents in *in vitro* RNase H and translation studies." (page 537) As stated in the abstract, "the arrays provide a simple empirical method of selecting effective antisense oligonucleotides for any RNA target of known sequence."

Milner et al. also state that "hetroduplex yield on the array correlated well with in vivo and in vitro cell culture antisense activities." (page 540) Milner et al. discusses a reference by Monia et al. (Nature Medicine (1996) 2:668-675; attached hereto as Appendix B), which identified an antisense inhibitor, ISIS 5132. (see page 669) ISIS 5132 was found to display "very potent inhibitory effects" in vivo (page 671) and was one of the antisense inhibitors that inhibited expression of C-raf in cell culture and in vivo.

(page 672) This antisense inhibitor was also found to show in vivo antitumor effects against two additional tumor cell lines. (page 672) Milner et al. conducted a blind experiment, performing analysis on a scanning array that picked out ISIS 5132 as one of two high-yielding oligonucleotides in a 100 b region around the oligonucleotide. (page 540)

Both Milner et al. and Monia et al. corroborate Applicant's submission that one of ordinary skill in the art would be able to determine effective antisense oligonucleotides capable of down-regulating gene expression without undue experimentation.

Furthermore, many published articles indicate that antisense oligonucleotides have been shown to be effective. For example, Galderisi et al. (J. Cell. Physiol. (1999) 181:251-57; attached as Appendix C), indicates that intravenous administration of phosphorothioate oligodeoxynucleotides showed effective and specific antisense inhibition in animal models, that antisense oligodeoxynucleotides have been shown to be effective in preclinical studies, and that some antisense oligodeoxynucleotides have reached clinical trials. The article also teaches that one drug based on antisense technology is now available in the United States. This article provides examples suggesting that "these compounds may have some therapeutic efficacy," including use as antiviral agents.

In addition, Agrawal states, at page v of Antisense Therapeutics, (Sudhir Agrawal, ed.) 1996, (cited pages of which were attached as Appendix D), that "[t]he results of preclinical studies using oligodeoxynucleotide phosphorothioates have shown that antisense oligonucleotides have good biological activity, pharmacology, pharmacokinetics, and safety both in vitro and in vivo, and they are currently being evaluated in human clinical trials for the treatment of viral infections and cancers."

Zamecnik (Antisense Therapeutics, (Sudhir Agrawal, ed.) (1996)) (also attached as Appendix E) states at page 6 of the same book that the synthetic antisense oligonucleotide technology displays promising results in cell-free systems, tissue

cultures, and animal models and is at early trial points in human testing against HIV, leukemia, Herpes virus, and other diseases.

Craig, et al. (Exp. Opin. Ther. Patents (1997) 7:1175-1182; attached as Appendix F) teaches at page 1177 that once a modification to the oligonucleotide backbone "is found to confer a favorable characteristic, it can then be used in oligonucleotides having different sequences of nucleosides and, thus, provide utility for the treatment of other diseases" as well as discussing information regarding the patentability of antisense technology.

In addition, the later-published work of Tortora, Wang, the symposium reference, and a press release by ISIS Pharmaceuticals discussed below corroborate the teachings of Applicant's specification and show that oligonucleotides described in the specification and administered according to the specification did successfully exhibit down-regulation of the expression of a gene in an animal.

More specifically, Tortora et al. (Clinical Cancer Research (2000) 6:2506-2512; attached as Appendix G), show that an antisense oligonucleotide having a methylphosphonate modification has antitumor activity in mice with GEO human colon cancer xenografts after oral administration, and that such treatment inhibited the expression of various proteins, including the target protein RIα.

Also, Wang et al. (PNAS (1999) 96:13989-13994; attached as Appendix H) show that an oligonucleotide containing 2'-O-alkyl ribonucleosides is orally bioavailable in mice and has had antitumor effects in SCID and nude mice with xenografts of various human cancers. Expression of the RIα subunit of PKA was shown to be decreased or down regulated as a result of treatment with the antisense oligonucleotide.

A reference distributed at the International Business Communications' Fourth Annual International Symposium on Oligonucleotide- & Gene Therapy-Based Antisense Therapeutics, held February 6-7, 1997 in San Diego, California (attached as Appendix I), demonstrates that 2'-O-alkoxyalkyl ribonucleotides, such as 2'-O-methoxyethyl-ribonucleotides, exhibit antitumor activity when administered orally and are orally bioavailable.

A press release (ISIS Pharmaceuticals; attached as Appendix J) discloses the outcome of studies regarding the oral formulation of antisense drugs.

This information clearly indicates that the specification enables the claimed invention by providing supportive data indicating that in vivo use of the invention has, in fact, been achieved.

Accordingly, based on the information provided in the published references described above, Applicant submits that (1) it would not require undue experimentation to find effective oligonucleotides capable of down-regulating gene expression, and (2) the claims cover only operable embodiments, and, as stated in M.P.E.P § 2164.03, "even in unpredictable arts [Applicant submits that this art is no longer unpredictable], a disclosure of every operable species is not required."

Therefore, Applicants respectfully submits that in view of the foregoing remarks and the corroborating references submitted herewith, pending claims 3 and 4 are enabled by the specification as filed. Accordingly, Applicant respectfully requests that the rejection of these claims under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.

5. ***Amended Claim 1 is Not Anticipated By Krieg et al. (WO 96/02555 or Antisense and Nucleic Acid Drug Devel. 6:133-135 (1996)).***

Claims 1 and 2 stand rejected under 35 U.S.C. § 102(a) as being anticipated by Krieg et al. (WO 96/02555 or Antisense and Nucleic Acid Drug Devel. 6:133-135 (1996)).

Applicant submits that the outstanding rejection under § 102(a) is rendered moot in view of the amendment of claim 1 to read on a modified CpG-containing phosphorothioate oligonucleotide, wherein the modification is selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG.

In view of the amendment, Applicant respectfully requests reconsideration and withdrawal of the outstanding rejection.

6. ***Amended Claim 1 is Not Anticipated By Krieg et al. (Nature 374:546-549 (1995)).***

Claim 1 stands rejected under 35 U.S.C. § 102(b) as being anticipated by Krieg *et al.*

Applicant submits that the amendment of claim 1 requested herein renders the outstanding rejection moot for the reasons stated *supra*. Accordingly, Applicant respectfully requests reconsideration and withdrawal of the outstanding rejection.

Conclusion

It is not believed that extensions of time or fees for net addition of claims are required beyond those that may otherwise be provided for in documents accompanying this paper. However, if additional extensions of time are necessary to prevent abandonment of this application, then such extensions of time are hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to our Deposit Account No. 08-0219.

In addition, pursuant to 37 C.F.R. § 1.136(a)(3), the Examiner is authorized to charge any fee under 37 C.F.R. § 1.17 applicable in the instant, as well as in future communications, to Deposit Account No. 08-0219. Such an authorization should be treated as a constructive petition for extension of time in the concurrent as well as future communications in the above-identified application.

Respectfully submitted,

Janice M. Klunder, Ph.D.
Reg. No. 41,121

Date: 10/4/02

HALE AND DORR L.L.P.
60 State Street
Boston, MA
Tel. (617) 526-6000
Fax (167) 526-5000

MARKED-UP VERSION OF THE CLAIM AMENDMENTS

1. (*Amended*) A composition [of matter] for inhibiting specific gene expression with reduced side effects, the composition comprising a modified CpG-containing phosphorothioate oligonucleotide that is complementary to a portion of a genomic region or gene for which inhibition of expression is desired, or to RNA transcribed from such a gene, wherein the modified CpG is selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG.

3. (*Amended*) A method for modulating gene expression in a mammal with reduced side effects comprising administering to the mammal a composition [of matter] according to claim 1, wherein the oligonucleotide is complementary to a gene that is being expressed in the mammal.

4. (*Amended*) A method for therapeutically treating, with reduced side effects, a disease caused by aberrant gene expression, the method comprising administering to an individual having the disease a composition [of matter] according to claim 1, wherein the oligonucleotide is complementary to a gene that is aberrantly expressed, wherein such aberrant expression causes the disease.

5. (*New*) A method for reducing side effects of a CpG-containing phosphorothioate oligonucleotide administered to a mammal, comprising:

(a) providing a CpG-containing phosphorothioate oligonucleotide having a CpG modification selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG; and

(b) administering the modified phosphorothioate oligonucleotide to the mammal,

wherein administration of the modified CpG-containing phosphorothioate oligonucleotide results in fewer side effects than the administration of an unmodified CpG-containing phosphorothioate oligonucleotide.

CLAIMS PENDING AFTER AMENDMENT ENTRY

1. (*Amended*) A composition for inhibiting specific gene expression with reduced side effects, the composition comprising a modified CpG-containing phosphorothioate oligonucleotide that is complementary to a portion of a genomic region or gene for which inhibition of expression is desired, or to RNA transcribed from such a gene, wherein the modified CpG is selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG.

3. (*Amended*) A method for modulating gene expression in a mammal with reduced side effects comprising administering to the mammal a composition according to claim 1, wherein the oligonucleotide is complementary to a gene that is being expressed in the mammal.

4. (*Amended*) A method for therapeutically treating, with reduced side effects, a disease caused by aberrant gene expression, the method comprising administering to an individual having the disease a composition according to claim 1, wherein the oligonucleotide is complementary to a gene that is aberrantly expressed, wherein such aberrant expression causes the disease.

5. (*New*) A method for reducing side effects of a CpG-containing phosphorothioate oligonucleotide administered to a mammal, comprising:

(a) providing a CpG-containing phosphorothioate oligonucleotide having a CpG modification selected from the group consisting of alkylphosphonate CpG, inverted CpG, 2'-O-substituted CpG, stereospecific phosphorothioate CpG, phosphotriester CpG, phosphoramidate CpG, and 2'-5' CpG; and

(b) administering the modified CpG-containing phosphorothioate oligonucleotide to the mammal, wherein administration of the modified CpG-containing phosphorothioate oligonucleotide results in fewer side effects than the administration of an CpG-containing unmodified phosphorothioate oligonucleotide.